

REMARKS

Claims 4 through 6 and 21 through 28 are pending, while claims 1-3 and 7 through 20 have been canceled.

The Office Action reportedly mailed February 2, 2004 has been received and reviewed. All of the pending claims were rejected. The application is to be amended as set forth. All amendments and claim cancellations are made without prejudice or disclaimer. No new matter has been added. Reconsideration is respectfully requested.

A. Earlier Response:

On November 10, 2003, applicants filed an amendment to the present Office Action. Evidently, the Office action signed by the Examiner on June 18, 2003 (and faxed to the undersigned on August 22, 2003) was only mailed on February 2, 2004. Since that amendment responded to an office action that had not yet been mailed, that amendment was deemed non-responsive, and is thus to be disregarded in its entirety.

B. Parallel Litigation / European Patent Office Oppositions:

In view of parallel litigation in the United Kingdom with respect to the corresponding European patent, applicants elect to cancel the non-process claims without prejudice or disclaimer. Applicants intend to prosecute a related application with the claims canceled herein at a later date.

Claims 4-6 and the other newly added process claims are not subject of the United Kingdom litigation. If more information regarding the U.K litigation is desired by the Examiner, she is kindly requested to contact the undersigned.

Further, in late January 2004, oppositions were also filed against the corresponding European patent. Copies of these opposition documents were filed with a Supplemental Information Disclosure Statement on March 3, 2004. An English language translation of the German language opposition of Helm AG is included herein for the convenience of the Examiner.

C. Claim Objections:

With respect to the February 2, 2004 office action, dependent claims 17 and 18 were objected to as allegedly failing to further limit claim 14. Although applicants do not agree with the objection, these claims have been canceled without prejudice or disclaimer, thus mooted the objection.

D. 35 U.S.C. § 102:

Claims 1-3, 7, and 9 were rejected as allegedly being anticipated by Sas et al. Although applicants do not agree with the rejection, these claims have been canceled without prejudice or disclaimer, thus mooted the rejection.

E. 35 U.S.C. § 103:

Claims 4-6 are rejected under 35 U.S.C. § 103 in view of Sas et al. and van Vliet et al. Applicants traverse the rejection. The newly added claims also depend on these claims and are addressed herein.

The Examiner relies on Examples 1-4 of Sas et al. for allegedly teaching a process in which crystals of the compound (seed crystals) are “aged” in the presence of water for one hour (*i.e.*, Example 2) and argues that it would have been obvious to a person of ordinary skill in the art at the time the invention was made to optimize the time period for “aging” crystals to at least 24 hours or 3-6 days.

Regarding an obviousness rejection, MPEP 2143 states:

To establish a *prima facie* case of obviousness, three basic criteria **must** be met. First, there must be some **suggestion or motivation**, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must **be a reasonable expectation of success**. Finally, the prior art reference (or references when combined) must teach or suggest **all the claim limitations**.

The Examiner relies on Roberts for the notion that the 1 hour period of Sas et al. can be extended to at least 24 hours, “since crystallization and recrystallization by optimizing variables, e.g., time, solvents, and temperature, **are well within the skill of the artisan** (see page 67-75).”

Applicants respectfully submit that the Examiner is applying an incorrect legal standard for obviousness, specifically admonished by the MPEP 2143 (2100-126):

**FACT THAT THE CLAIMED INVENTION IS WITHIN
THE CAPABILITIES OF ONE OF ORDINARY SKILL IN
THE ART IS NOT SUFFICIENT BY ITSELF TO
ESTABLISH PRIMA FACIE OBVIOUSNESS**

(emphasis in original). A general showing of possible modification by one of skill in the art is insufficient for a *prima facie* case of obviousness. In *In re Irani*, 166 U.S.P.Q. (BNA) 24 (C.C.P.A. 1966) claims to a crystalline anhydrous form of tri(methylenephosphonic acid) (“ATMP”) were initially rejected over a primary reference (Petrov) disclosing a glassy form of the same chemical compound in combination with secondary references that taught that other amino phosphonic acids exist in crystalline form. The Examiner in that case took the position that one would be motivated to attempt the preparation of crystalline anhydrous ATMP by knowledge that some amino phosphonic acids exist in crystalline form. The Examiner also observed that only a little modification of the Petrov process for making the glassy material was required to produce a crystalline material. The Board affirmed the Examiner’s rejection, but on the rationale that the physical properties of the known form suggested that it was impure and thus motivated one skilled in the art to attempt preparation of a purer form. The applicants argued on appeal, *inter alia*, that Petrov did not suggest that ATMP could exist in a crystalline form and that it was not expected that an anhydrous form of ATMP could be obtained in view of the teaching of prior publications that similar materials crystallize as mono or disolvates. The Court of Customs Patent Appeals held that even if the existence of crystalline ATMP were predictable from the references, the references did not teach a method by which it could be made:

As stated above, even assuming that one skilled in the art could have predicted with reasonable certainty that crystalline anhydrous ATMP could be produced, we are not convinced by this record that it would also have been obvious how this could be achieved. We note that neither the examiner nor the board has contended that a suitable process would have been obvious. **The closest that either has come to such a contention is the examiner's statement, based on the disclosure in the Irani patent, that, as it turns out, "little modification of the Petrov process will produce a crystalline material." Obviousness, however, must not be judged by hindsight, and a "little modification" can be a most unobvious one.**

The Examiner cites pages 67-75 of Roberts. Crystallization is only mentioned in pages 70 and 71 of Roberts. These pages however merely give tips to one of skill in the art on crystallization, such as whether to agitate or to seed the solution. Roberts does not state that crystallization followed by drying after at least 24 hours of the crystallization is desirable to obtain higher purity with regard to any compound, let alone tibolone. At most, Roberts provides general guidance on various factors involved in crystallization, which is not sufficient to provide motivation to delay drying by at least 24 hours.

Also, a difference exists between aging in the presence of an aqueous solvent and crystallizing from an aqueous solvent. In the case of tibolone, crystallization typically does not take more than one hour, whereas aging of tibolone crystals in accordance with the present invention takes at least 24 hours and most suitably should be carried out for a period of time of 3-6 days. The skilled person would generally filter off, wash, and dry the crystals as soon as sufficient crystals had been formed. As acknowledged in the Office Action, Sas et al., particularly in Example 2, teaches a time period of one hour for allowing the crystals to form or to grow before the crystals are filtered off, washed, and dried. However, in Example 4, starting with 2.3 kg of polymorphous tibolone versus 1 kg of polymorphous tibolone in Example 2, a time period of only 15 minutes is taught for forming the crystals. If anything, Sas et al. teaches that crystallization of tibolone is complete or sufficiently complete after a period of time of from 15 minutes to one hour. Furthermore, Sas et al. teaches nothing with respect to increasing the

time the formed crystals remain in the mixture resulting from crystallization. This is what the presently claimed invention is about. Where the skilled person would ordinarily filter off, wash, and dry the crystals once sufficient crystals had been formed, in accordance with the presently claimed invention, he or she is taught to wait for at least 24 hours before doing so, which is uncommon and not taught by the prior art referred to by the Examiner.

The Examiner treats crystallization as a predictable art. Applicants note that polymorphism/solid state chemistry/crystallization is an unpredictable art. Although general techniques for preparing crystals are known, there is no accurate way even to determine that a particular isolation technique will produce a particular crystal. Even Roberts states that crystallization gives different crystals depending on the conditions used. The Examiner's position that crystallization may be modified within the skill of art does not take into account that such modification may result in a solid having high impurity.

Here, as a result of aging in accordance with the invention, crystals of tibolone are obtained with a higher purity and with a better stability as illustrated by comparing the results of (comparative) Example 1 with Example 2 in the specification. Nothing in the art would suggest or have predicted this unexpected result (or applicants' claimed process), and applicants accordingly request that the rejection be withdrawn.

The newly added dependent claims have additional features. The art does not teach or suggest waiting at least 24 hours after washing of the crystals to dry (claim 21), or performing the washing after filtering (claim 24) followed by drying after at least 24 hours.

If it would be considered helpful to the Office, applicants are willing to schedule an interview with the examiner to facilitate the prosecution of the instant application.


F. 35 U.S.C. § 103:

Claims 10, 11, and 13-20 were rejected as being unpatentable under 35 U.S.C. § 103 in view of Sas et al., van Vliet et al. and de Haan. Although applicants do not agree, these claims have been canceled without prejudice or disclaimer, thus mooting the rejection.

Conclusion

In view of the foregoing, the application should be in condition for allowance. If questions should remain after consideration of the foregoing, however, the Office is kindly requested to contact applicants' attorney at the address or telephone number given herein.

Respectfully submitted,

A handwritten signature in black ink, appearing to read 'Allen C. Turner', with a long horizontal flourish extending to the right.

Allen C. Turner

Registration No. 33,041

Attorney for Applicants

TRASKBRITT, P.C.

P.O. Box 2550

Salt Lake City, Utah 84110-2550

Telephone: 801-532-1922

Facsimile: 801-531-9168

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